

A Hyper-Crosslinked Carbohydrate Polymer Scaffold Facilitates Lineage Commitment and Maintains a Reserve Pool of Proliferating Cardiovascular Progenitors.

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Public Summary:

Cardiovascular progenitor cells (CPCs) have been cultured on various scaffolds to resolve the challenge of cell retention after transplantation and to improve functional outcome after cell-based cardiac therapy. Previous studies have reported successful culture of fully differentiated cardiomyocytes on scaffolds of various types, and ongoing efforts are focused on optimizing the mix of cardiomyocytes and endothelial cells as well as on the identification of a source of progenitors capable of reversing cardiovascular damage. A scaffold culture that fosters cell differentiation into cardiomyocytes and endothelial cells while maintaining a progenitor reserve would benefit allogeneic cell transplantation

Scientific Abstract:

BACKGROUND: Cardiovascular progenitor cells (CPCs) have been cultured on various scaffolds to resolve the challenge of cell retention after transplantation and to improve functional outcome after cell-based cardiac therapy. Previous studies have reported successful culture of fully differentiated cardiomyocytes on scaffolds of various types, and ongoing efforts are focused on optimizing the mix of cardiomyocytes and endothelial cells as well as on the identification of a source of progenitors capable of reversing cardiovascular damage. A scaffold culture that fosters cell differentiation into cardiomyocytes and endothelial cells while maintaining a progenitor reserve would benefit allogeneic cell transplantation. **METHODS:** Isl-1 + c-Kit + CPCs were isolated as clonal populations from human and sheep heart tissue. After hyper-crosslinked carbohydrate polymer scaffold culture, cells were assessed for differentiation, intracellular signaling, cell cycling, and growth factor/chemokine expression using real time polymerase chain reaction, flow cytometry, immunohistochemistry, and calcium staining. **RESULTS:** Insulin-like growth factor 1, hepatocyte growth factor, and stromal cell derived factor 1alpha paracrine factors were induced, protein kinase B signaling was activated, extracellular signal-regulated kinase phosphorylation was reduced and differentiation into both cardiomyocytes and endothelial cells was induced by scaffold-based cell culture. Interestingly, movement of CPCs out of the G1 phase of the cell cycle and increased expression of pluripotency genes PLOU5F1 (Oct4) and T (Brachyury) within a portion of the cultured population occurred, which suggests the maintenance of a progenitor population. Two-color immunostaining and 3-color fluorescence-activated cell sorting analysis confirmed the presence of both Isl-1 expressing undifferentiated cells and differentiated cells identified by troponin T and von Willebrand factor expression. Ki-67 labeling verified the presence of proliferating cells that remained in situ alongside the differentiated functional derivatives. **CONCLUSIONS:** Cloned Isl-1 + c-kit + CPCs maintained on a hyper-cross linked polymer scaffold retain dual potential for proliferation and differentiation, providing a scaffold-based stem cell source for transplantation of committed and proliferating cardiovascular progenitors for functional testing in preclinical models of cell-based repair.

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